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Attorney Docket No. 35800/204489 (5800-28A)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Robison *et al.*		
Appl. No.:	09/668,266	Group Art Unit:	1655
Filed:	September 22, 2000	Examiner:	B. Sisson
For:	22025, A NOVEL HUMAN CYCLIC NUCLEOTIDE PHOSPHODIESTERASE		

July 2, 2001

Commissioner for Patents
Washington, DC 20231

AMENDMENT

Sir:

In response to the Office Action mailed March 30, 2001, please amend the above-identified application as follows:

In The Specification:

Please amend the paragraph on page 6, lines 6-11, to read as follows:

The invention is thus based on the identification of a novel human cyclic nucleotide phosphodiesterase. The invention encompasses a long and short form of the phosphodiesterase. The amino acid sequence of the longer form is shown in SEQ ID NO:1 and the amino acid sequence of the shorter form is shown as SEQ ID NO:3. The nucleotide sequence of the longer form is shown as SEQ ID NO:2 or SEQ ID NO:4 and the nucleotide sequence of the shorter form is shown as SEQ ID NO:4.

Please amend the paragraph on page 6, lines 12-16, to read as follows:

The invention provides isolated phosphodiesterase polypeptides, including a polypeptide having the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or the amino acid sequence encoded by the cDNA deposited as ATCC No. PTA-1644 on April 5, 2000 ATCC.

01 FC:103 306.00 CH

07/10/2001 MYUSUF1 00000027 09668266

01 FC:103 90.00 OP
02 FC:102 320.00 OP

Please amend the paragraph on page 6, lines 17-19, to read as follows:

The invention also provides isolated phosphodiesterase nucleic acid molecules having the sequence shown in SEQ ID NO:2 or SEQ ID NO:4 or in the deposited cDNA.

Please amend the paragraph on page 6, lines 20-22, to read as follows:

The invention also provides variant polypeptides having an amino acid sequence that is substantially homologous to the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3 or encoded by the deposited cDNA.

B1

Please amend the paragraph on page 6, lines 23-25, to read as follows:

The invention also provides variant nucleic acid sequences that are substantially homologous to the nucleotide sequence shown in SEQ ID NO:2 or SEQ ID NO:4 or in the deposited cDNA.

Please amend the paragraph on page 6, lines 26-28, to read as follows:

The invention also provides fragments of the polypeptide shown in SEQ ID NO:1 or SEQ ID NO:3 and nucleotide sequence shown in SEQ ID NO:2 or SEQ ID NO:4, as well as substantially homologous fragments of the polypeptide or nucleic acid.

Please amend the paragraph on page 7, lines 26-29, to read as follows:

B2

Figure 1 shows the long phosphodiesterase nucleotide sequence (SEQ ID NO:2) and the deduced amino acid sequence (SEQ ID NO:1). It is predicted that amino acids 1-223 constitute the aminoterminal regulatory domain, amino acids 224-462 constitute the catalytic domain, and amino acids 463-502 constitute the carboxyterminal domain.

Please amend the paragraph on page 9, lines 4-7, to read as follows:

B3

Figure 6 shows the short phosphodiesterase nucleotide sequence (SEQ ID NO:4) and the deduced amino acid sequence (SEQ ID NO:3). It is predicted that amino acids 1-223 constitute the amino terminal regulatory domain, and amino acids 224-320 constitute the catalytic domain.

Please amend the paragraph on page 11, lines 10-13, to read as follows:

B4 The invention thus relates to a novel phosphodiesterase having the deduced amino acid sequence shown in Figure 1 or Figure 6 (SEQ ID NO:1 or SEQ ID NO:3) or having the amino acid sequence encoded by the deposited cDNA, ATCC No. PTA-1644.

Please amend the paragraph on page 11, lines 20-24, to read as follows:

B5 "Phosphodiesterase polypeptide" or "phosphodiesterase protein" refers to the polypeptides in SEQ ID NO:1 or SEQ ID NO:3 or encoded by the deposited cDNAs. The term "phosphodiesterase protein" or "phosphodiesterase polypeptide", however, further includes the numerous variants described herein, as well as fragments derived from the full-length phosphodiesterases and variants.

Please amend the paragraph on page 12, lines 3-5, to read as follows:

B6 The phosphodiesterases include a catalytic signature, HDVDHPG, at residues 265-271. The sequence includes HDXXHXX (SEQ ID NO:40), a consensus amino acid sequence in cyclic nucleotide phosphodiesterases.

Please amend the paragraph on page 13, lines 9-26, to read as follows:

B7 In one embodiment, the phosphodiesterase polypeptide comprises the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3. However, the invention also encompasses sequence variants. Variants include a substantially homologous protein encoded by the same genetic locus in an organism, i.e., an allelic variant. The phosphodiesterase has been mapped to human chromosome 6 (6q21-q23.2), with flanking markers AFMA074ZG9 (2.6cR) and AFM214ZF6 (7.9cR). Mutations near this locus include, but are not limited to, the following: PPAC, arthropathy, progressive pseudorheumatoid, of childhood; ODDD, oculodentodigital dysplasia; heterocellular hereditary persistence of fetal hemoglobin; DFNA10, deafness, autosomal dominant nonsyndromic sensorineural 10; CMD1F, cardiomyopathy, dilated, 1F; and diabetes mellitus, transient neonatal. In the mouse this locus is associated with the following: gl, grey-lethal; dl, downless; Cat5, dominant

cataract 5; Lwq3, liver weight QTL 3; mshi, male sterility and histoincompatibility; Mop2, morphine preference 2; H60, histocompatibility 60; Daq4, directional asymmetry QTL 4; Daq5, directional asymmetry QTL 5; and kd / kidney disease. Genes near this locus include PDNP1 (phosphodiesterase l/nucleotide pyrophosphatase 1 (homologous to mouseLy-41 antigen)), MACS, PTPRK, ARG1, PCMT1, DFNA10, MEKK5, CTGF, SGK, HIVEP2, CMD1F, EPB41L2, HPFH, UTRN, IFNGR1, and ESR1.

Please amend the paragraph on page 13, line 27 to page 14, line 3, to read as follows:

B7 cont.

Variants also encompass proteins derived from other genetic loci in an organism, but having substantial homology to the phosphodiesterase of SEQ ID NO:1 or SEQ ID NO:3. Variants also include proteins substantially homologous to the phosphodiesterase but derived from another organism, i.e., an ortholog. Variants also include proteins that are substantially homologous to the phosphodiesterase that are produced by chemical synthesis. Variants also include proteins that are substantially homologous to the phosphodiesterase that are produced by recombinant methods. It is understood, however, that variants exclude any amino acid sequences disclosed prior to the invention.

Please amend the paragraph on page 14, lines 4-10, to read as follows:

B8

As used herein, two proteins (or a region of the proteins) are substantially homologous when the amino acid sequences are at least about 70-75%, typically at least about 80-85%, and most typically at least about 90-95% or more homologous. A substantially homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid sequence hybridizing to the nucleic acid sequence, or portion thereof, of the sequence shown in SEQ ID NO:2 or SEQ ID NO:4 under stringent conditions as more fully described below.

Please amend the paragraph on page 17, lines 1-8, to read as follows:

B9

A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.* (1993) *Proc. Natl. Acad. Sci.* USA *90*:5873-5877. Such an algorithm is incorporated into the

NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.* (1997) *Nucleic Acids Res. 25*:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., NBLAST) can be used. See http://www.ncbi.nlm.nih.gov. In one embodiment, parameters for sequence comparison can be set at score = 100, wordlength = 12, or can be varied (e.g., W = 5 or W = 20).

Please amend the paragraph on page 17, lines 9-18, to read as follows:

B9 cont.

In a preferred embodiment, the percent identity between two amino acid sequences is determined using the Needleman *et al.* (1970) (*J. Mol. Biol. 48*:444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at http://www.gcg.com), using either a BLOSUM 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (Devereux *et al.* (1984) *Nucleic Acids Res. 12*(1):387) (available at http://www.gcg.com), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6.

Please amend the paragraph on page 19, lines 8-11, to read as follows:

B10

The invention thus also includes polypeptide fragments of the phosphodiesterase. Fragments can be derived from the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3. However, the invention also encompasses fragments of the variants of the phosphodiesterases as described herein.

Please amend the paragraph on page 25, lines 4-16, to read as follows:

B11

The protein sequences of the present invention can be used as a "query sequence" to perform a search against public databases to, for example, identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403-10. BLAST nucleotide searches can

be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to the nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

B11 cont.

Please amend the paragraph on page 38, lines 20-24, to read as follows:

The nucleotide sequences in SEQ ID NO:2 or SEQ ID NO:4 were obtained by sequencing the deposited human cDNA. Accordingly, the sequence of the deposited clone is controlling as to any discrepancies between the two and any reference to the sequences of SEQ ID NO 2 or SEQ ID NO 4 includes reference to the sequences of the deposited cDNA.

B12

[Please amend the paragraph on page 38, lines 25-26, to read as follows:]

The specifically disclosed cDNAs comprise the coding region and 5' and 3' untranslated sequences in SEQ ID NO:2 or SEQ ID NO:4.

Please amend the paragraph on page 39, lines 1-6, to read as follows:

The invention provides isolated polynucleotides encoding the novel phosphodiesterases. The term "phosphodiesterase polynucleotide" or "phosphodiesterase nucleic acid" refers to the sequences shown in SEQ ID NO:2 or SEQ ID NO:4 or in the deposited cDNAs. The term "phosphodiesterase polynucleotide" or "phosphodiesterase nucleic acid" further includes variants and fragments of the phosphodiesterase polynucleotides.

B13

Please amend the paragraph on page 41, lines 1-3, to read as follows:

Phosphodiesterase nucleic acid can comprise the nucleotide sequences shown in SEQ ID

B14

B14 cont. NO:2 or SEQ ID NO:4, corresponding to human osteoblast (short form) and kidney and adrenal gland (long form) cDNA.

Please amend the paragraph on page 41, lines 6-9, to read as follows:

B15 The invention further provides variant phosphodiesterase polynucleotides, and fragments thereof, that differ from the nucleotide sequences shown in SEQ ID NO:2 or SEQ ID NO:4 due to degeneracy of the genetic code and thus encode the same protein as that encoded by the nucleotide sequences shown in SEQ ID NO:2 or SEQ ID NO:4.

Please amend the paragraph on page 41, lines 18-21, to read as follows:

Typically, variants have a substantial identity with a nucleic acid molecules of SEQ ID NO:2 or SEQ ID NO:4 and the complements thereof. Variation can occur in either or both the coding and non-coding regions. The variations can produce both conservative and non-conservative amino acid substitutions.

[Please amend the paragraph on page 41, line 22 to page 42, line 2, to read as follows:]

B16 Orthologs, homologs, and allelic variants can be identified using methods well known in the art. These variants comprise a nucleotide sequence encoding a phosphodiesterase that is at least about 60-65%, 65-70%, typically at least about 70-75%, more typically at least about 80-85%, and most typically at least about 90-95% or more homologous to the nucleotide sequence shown in SEQ ID NO:2 or SEQ ID NO:4 or a fragment of this sequence. Such nucleic acid molecules can readily be identified as being able to hybridize under stringent conditions, to the nucleotide sequence shown in SEQ ID NO:2 or SEQ ID NO:4 or a fragment of the sequence. It is understood that stringent hybridization does not indicate substantial homology where it is due to general homology, such as poly A sequences, or sequences common to all or most proteins, all cyclic nucleotide phosphodiesterases, or all Family 7 phosphodiesterases. Moreover, it is understood that variants do not include any of the nucleic acid sequences that may have been disclosed prior to the invention.

Please amend the paragraph on page 42, lines 3-23, to read as follows:

As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences encoding a polypeptide at least about 60-65% homologous to each other typically remain hybridized to each other. The conditions can be such that sequences at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 90%, at least about 95% or more identical to each other remain hybridized to one another. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6, incorporated by reference. One example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50-65°C. In another non-limiting example, nucleic acid molecules are allowed to hybridize in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more low stringency washes in 0.2X SSC/0.1% SDS at room temperature, or by one or more moderate stringency washes in 0.2X SSC/0.1% SDS at 42°C, or washed in 0.2X SSC/0.1% SDS at 65°C for high stringency. In one embodiment, an isolated nucleic acid molecule that hybridizes under stringent conditions to the sequence of SEQ ID NO:1 or SEQ ID NO:3 corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).

Please amend the paragraph on page 42, line 32 to page 43, line 9, to read as follows:

The present invention also provides isolated nucleic acids that contain a single or double stranded fragment or portion that hybridizes under stringent conditions to the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4 or the complement of SEQ ID NO:2 or SEQ ID NO:4. In one embodiment, the nucleic acid consists of a portion of the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4 and the complement of SEQ ID NO:2 or SEQ ID NO:4. The nucleic acid fragments of the invention are at least about 15, preferably at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200, 500 or more nucleotides in length. Longer

B18 cont. fragments, for example, 30 or more nucleotides in length, which encode antigenic proteins or polypeptides described herein are useful.

Please amend the paragraph on page 44, lines 10-20, to read as follows:

The nucleotide sequences of the present invention can be used as a "query sequence" to perform a search against public databases, for example, to identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul *et al.* (1990) *J. Mol. Biol. 215*:403-10. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the proteins of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res. 25(17)*:3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See http://www.ncbi.nlm.nih.gov.

B19

Please amend the paragraph on page 44, lines 21-30, to read as follows:

The nucleic acid fragments of the invention provide probes or primers in assays such as those described below. "Probes" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid. Such probes include polypeptide nucleic acids, as described in Nielsen *et al.* (1991) *Science 254*:1497-1500. Typically, a probe comprises a region of nucleotide sequence that hybridizes under highly stringent conditions to at least about 15, typically about 20-25, and more typically about 40, 50 or 75 consecutive nucleotides of the nucleic acid sequence shown in SEQ ID NO:2 or SEQ ID NO:4 and the complements thereof. More typically, the probe further comprises a label, e.g., radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

Please amend the paragraph on page 45, lines 19-28, to read as follows:

B20

The phosphodiesterase polynucleotides are useful as a hybridization probe for cDNA and

genomic DNA to isolate a full-length cDNA and genomic clones encoding the polypeptides described in SEQ ID NO:1 or SEQ ID NO:3 and to isolate cDNA and genomic clones that correspond to variants producing the same polypeptides shown in SEQ ID NO:1 or SEQ ID NO:3 or the other variants described herein. Variants can be isolated from the same tissue and organism from which the polypeptides shown in SEQ ID NO:1 or SEQ ID NO:3 were isolated, different tissues from the same organism, or from different organisms. This method is useful for isolating genes and cDNA that are developmentally-controlled and therefore may be expressed in the same tissue or different tissues at different points in the development of an organism.

B20 cont.

Please amend the paragraph on page 46, lines 4-7, to read as follows:

B21

The nucleic acid probe can be, for example, the full-length cDNA of SEQ ID NO:2 or SEQ ID NO:4, or a fragment thereof, such as an oligonucleotide of at least 12, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to mRNA or DNA.

Please amend the paragraph on page 46, line 14 to page 47, line 6, to read as follows:

B22

Antisense nucleic acids of the invention can be designed using the nucleotide sequences of SEQ ID NO:2 or SEQ ID NO:4, and constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (e.g., an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, e.g., phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-

methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been subcloned in an antisense orientation (i.e., RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest).

B22 cont.

Please amend the paragraph on page 60, lines 1-5, to read as follows:

Examples of antisense molecules useful to inhibit nucleic acid expression include antisense molecules complementary to a fragment of the 5' untranslated region of SEQ ID NO:2 or SEQ ID NO:4 which also includes the start codon and antisense molecules which are complementary to a fragment of the 3' untranslated region of SEQ ID NO:2 or SEQ ID NO:4.

B23

In The Claims:

Please cancel claim 1 without prejudice to or disclaimer of the subject matter contained therein.

Please insert the following new claims:

B24

--19. An isolated polypeptide having an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3; and

(b) the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. PTA-1644.

20. The isolated polypeptide of claim 19 comprising the amino acid sequence of SEQ

ID NO:1 or SEQ ID NO:3.

21. The polypeptide of claim 19 further comprising heterologous amino acid sequences.

22. An antibody that selectively binds to a polypeptide of claim 19.

23. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3.

24. The polypeptide of claim 23 further comprising heterologous amino acid sequences.

25. An antibody that selectively binds to the polypeptide of claim 23.

26. A polypeptide comprising a fragment of the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3, wherein the fragment has a kinase protein activity and comprises at least 75 contiguous amino acids of SEQ ID NO:1 or SEQ ID NO:3.

27. The polypeptide of claim 26 further comprising heterologous amino acid sequences.

28. An antibody that selectively binds to the polypeptide of claim 26.

29. A polypeptide having a phosphodiesterase activity, wherein said polypeptide is encoded by a nucleic acid molecule comprising a nucleotide sequence having at least 80% sequence identity to the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4.

30. The polypeptide of claim 29 further comprising heterologous amino acid sequences.

31. An antibody that selectively binds to the polypeptide of claim 29.

32. The polypeptide of claim 29 wherein said polypeptide is encoded by a nucleic acid molecule comprising a nucleotide sequence having at least 90% sequence identity to the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4.

33. The polypeptide of claim 32 wherein said polypeptide is encoded by a nucleic acid molecule comprising a nucleotide sequence having at least 95% sequence identity to the nucleotide sequence of SEQ ID NO:2 or SEQ ID NO:4.

34. A polypeptide having a phosphodiesterase activity, wherein the polypeptide is encoded by a nucleic acid molecule that hybridizes to a nucleic acid molecule comprising the sequence encoded by the cDNA contained in ATCC Deposit No. PTA-1644 under stringent conditions, said stringent conditions comprising hybridization in 6 X SSC at 42°C, followed by washing with 1 X SSC at 55°C.

35. The polypeptide of claim 34 further comprising heterologous amino acid sequences.

36. An antibody that selectively binds to the polypeptide of claim 34.

37. An isolated polypeptide having an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of an allelic variant of the amino acid sequence shown in SEQ ID NO 1 or SEQ ID NO 3;

(b) the amino acid sequence of an allelic variant of the amino acid sequence encoded by the cDNA contained in ATCC Deposit No.PTA-1644;

(c) the amino acid sequence of a sequence variant of the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3, wherein the sequence variant is encoded by a nucleic acid molecule hybridizing to the nucleic acid molecule shown in SEQ ID NO:2 or SEQ ID NO:4 under stringent conditions wherein said stringent conditions comprise allowing nucleic acid molecules to hybridize in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC/0.1% SDS at 65°C;

(d) the amino acid sequence of a sequence variant of the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No.PTA-1644, wherein the sequence variant is encoded by a nucleic acid molecule hybridizing under said stringent conditions to the cDNA contained in ATCC Deposit No. PTA-1644;

(e) a fragment of the amino acid sequence shown in SEQ ID NO:1 or SEQ ID NO:3, wherein the fragment comprises at least 50 contiguous amino acids;

(f) a fragment of the amino acid sequence encoded by the cDNA contained in ATCC Deposit No. PTA-1644, wherein the fragment comprises at least 50 contiguous amino acids;

(g) the amino acid sequence of the mature polypeptide from about amino acid 6 to the last amino acid shown in SEQ ID NO:1 or SEQ ID NO:3;

(h) the amino acid sequence of the mature polypeptide from about amino acid 6 to the last amino acid encoded by the cDNA clone contained in ATCC Deposit No. PTA-1644; and

(i) the amino acid sequence of an epitope bearing region of any one of the polypeptides of (a)-(h).

38. The isolated polypeptide of claim 37 comprising the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3.

39. The polypeptide of claim 37 further comprising heterologous amino acid sequences.

40. An antibody that selectively binds to a polypeptide of claim 37.

41. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:3.

42. The polypeptide of claim 41 further comprising heterologous amino acid sequences.

43. An antibody that selectively binds to the polypeptide of claim 42.--

REMARKS

Status of the Claims:

Claims 19-43 are pending in the application. The Examiner rejected Claim 1 and withdrew Claims 2-18 from consideration. Claim 1 has been deleted and replaced with new Claims 19-43. Support for the new claims can be found in the specification, particularly pages 6-7, 11-21, and 38-44, as well as the original claims. No new matter has been added by way of amendment.

Objections to the Specification

The specification has been objected to for containing embedded hyperlinks and/or other forms of browser-executable code. Applicant has amended the specification to remove these embedded hyperlinks, thereby obviating this objection.

The specification has also been objected to for failing to provide ATCC deposit numbers. Applicant has amended the specification to include the required ATCC deposit numbers, thereby obviating this objection.

The specification was also objected to for including blank lines in the disclosure on page 11, as well as including amino acid sequences unaccompanied by their requisite SEQ ID NO's on page 12. Applicant has amended the specification to incorporate the deposit information, eliminating the blank lines, and to insert the requested SEQ ID NO, thereby obviating this objection.

The Rejections Under 35 U.S.C. §112, First Paragraph Should be Withdrawn

Claim 1 was rejected under 35 U.S.C. §112, first paragraph on the grounds that it contained subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that, at the time the application was filed, the inventors had possession of the claimed invention. On substantially the same grounds, Claim 1 was also rejected under 35 U.S.C. §112, first paragraph on the basis that the embodiment set forth in 1(e) and 1(f) is that of a product-by-process, but that this does not relieve the Applicant of the requirement of having first possessed the now claimed invention. These rejections are respectfully traversed for the reasons described below.

The Examiner states that the Applicant is claiming a genus of compounds but has only provided an adequate description of two species, represented by SEQ ID NO: 1 and SEQ ID NO: 3. For each claim drawn to a genus, the written description requirement may be satisfied through a sufficient description of a representative number of species identifying characteristics sufficient to show the applicant was in possession of the claimed genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1406 (Fed. Cir. 1997). Thus, there are two related elements of the written description requirement: 1) sufficient description; and 2) a representative number of species.

Sufficient description can be shown by disclosure of relevant, identifying characteristics, (*i.e.,* structure or other physical and/or chemical properties). *Id.*; *see also* 66 Fed. Reg. 1099, 1106 (2000). The present invention is described on page 13, lines 9-11 of the specification as a phosphodiesterase polypeptide comprising not only the amino acid sequence shown in SEQ ID NO:

1 or SEQ ID NO: 3, but also sequence variants encompassing substantially homologous proteins. Relevant identifying physical and chemical properties of the disclosed genus are provided on page 14, lines 4-10 of the specification where substantially homologous proteins are further defined as having amino acid sequences that are most typically at least about 90-95% or more homologous and are encoded by a nucleic acid sequence hybridizing to the nucleic acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4 under stringent conditions. Further identifying physical and chemical properties of the disclosed genus are provided by the limitations incorporated into new independent Claims 34 and 37, wherein single embodiments of stringent conditions are recited, as described below. Because of the description of these physical and chemical properties of the disclosed genus, Applicant respectfully asserts that a sufficient description of the current invention has been shown.

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2000). The Examiner states that the Applicant has only provided an adequate description of two species, represented by SEQ ID NO: 1 and SEQ ID NO: 3. In fact, the specification also describes on page 11, lines 10-13 that the present invention encompasses the amino acid sequence encoded by the deposited cDNA that was used to obtain the nucleotide sequences in SEQ ID NO: 2 and SEQ ID NO: 4. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. 66 Fed. Reg. 1099, 1106 (2000). In the present invention, the common attributes or features of the elements possessed by the members of the genus is that they are encoded by a nucleic acid sequence hybridizing to the nucleic acid sequence shown in SEQ ID NO: 2 or SEQ ID NO: 4 under stringent conditions. One of ordinary skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Therefore, Applicant respectfully asserts that a representative number of species has been described.

The Examiner further states that Claim 1 was rejected under 35 U.S.C. §112, first paragraph on the grounds that it has not satisfied the written description requirement since elements 1(d); 1(f); and 1(k) all rely upon the availability of deposited material. The deposit information has been inserted into the specification and claims, thereby obviating this rejection.

Claim 1 was also rejected under 35 U.S.C. §112, first paragraph on the grounds that it contained subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. For the reasons set forth below, this rejection is respectfully traversed.

The Examiner states that Applicant is claiming compounds neither described nor apparently in their possession at the time of filing, and that it is impossible to enable the use of compounds one does not possess. As previously addressed, Applicant respectfully asserts that the subject matter of the present invention was described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Therefore, Examiner's argument on these grounds has been obviated.

The Examiner further states that the specification has not set forth in full and complete terms how such compounds will be used without inviting undue experimentation. Applicants have provided many particular citations in the application which support Applicants' assertions of utility and operability; (see, for example, pages 25-34 of the specification) further, those of skill in the art are familiar with routine techniques which enable those of skill to use the present invention in the asserted utilities. See, for example, C. Wagener, *Molecular diagnostics*, 75 J. Mol. Med. 728 (1997); U. Landegren and M. Nilsson, *Locked on target: strategies for future gene diagnostics*, 29 Ann. Med. 585 (1997); M. G. Rusnak, *Biotechnology of diagnostics: emerging opportunities*, 13 Biotechnology 1056 (1995). Applicant notes that "where those of ordinary skill in the art will know how to use, the applicant has a right to rely on such knowledge." *In re Nelson*, 280 F.2d 172, 184 (C.C.P.A. 1960).

Applicant believes that the Office Action has mistakenly confounded the §101 standard with the §112 standard, to the detriment of Applicant. It is true that "[t]he lack of utility because of inoperativeness (a question of fact), and the absence of enablement (a question of law) are closely related grounds of unpatentability." *Ex parte Dash*, 27 U.S.P.Q.2d 1481, 1484 (Bd. Pat. App. & Int'f 1993). However, here, the Examiner indicates that "While the specification has been found to provide a listing of possible uses, such suggestions rather than rising to the level of enabling disclosure, constitute only an invitation for others to experiment." (March 30, 2001, Office Action (p. 6)). Thus, here, as in *In re Nelson*, 280 F.2d 172 (C.C.P.A. 1960), overruled in part by *In re Kirk*, 376 F.2d 936 (C.C.P.A. 1967), the Examiner has incorrectly "taken the position that appellants have not complied with § 112, but it has not shown why this is so except by objection to the kind of utility disclosed, which presents an issue under §101 rather than §112." 280 F.2d at 177. Further, "what the Patent Office is really trying to insist on here has nothing to do with the 'how to use' provision of §112. It is demanding some different, or greater, or more commercial or more mundane use than the one disclosed." *Id.* at 183. Finally, the *Nelson* court said: "[m]uch confused thinking on this matter has resulted from a failure to separate the requirement of §101 that an invention be useful from the §112 requirement that the specification shall so explain 'the manner and processes of ... using' the invention as to 'enable any person skilled in the art ... to ... use the same.'" *Id.* at 184.

Applicant notes that claims are presumed to be enabled under §112: "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971). "Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling." *Id.* at 223. Applicant contends that here, there is no reason to

doubt Applicant's assertions concerning enablement; one of skill in the art would be able to make and use the claimed invention with only the exercise of routine practices, as discussed above. The Examiner has not advanced sufficient grounds for questioning the accuracy of Applicant's statements and the rejection under §112 should be withdrawn.

In view of these arguments, the rejection of the claims under 35 U.S.C. §112, first paragraph, have been overcome and should be withdrawn.

The Rejection Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn

Claim 1 was rejected under 35 U.S.C. §112, second paragraph on the grounds that the phrase "stringent conditions" is unclear. This rejection is respectfully traversed. The specification does provide guidance regarding what is meant by "stringent conditions" on page 42, lines 3-22. Furthermore, new independent Claims 34 and 37 recite single embodiments of stringent conditions. Support for these claims may be found on page 42, lines 11-18 of the specification.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

W. Murray Spruill
Registration No. 32,943

ALSTON & BIRD LLP
Post Office Drawer 34009
Charlotte, NC 28234
Tel Raleigh Office (919) 420-2200
Fax Raleigh Office (919) 420-2260

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